

(Krumholz *et al.*, 2007). When the truth of the real risks emerged, the drug was withdrawn. Systematic reviews serve to foster such enlightenment.

We agree with Rees' description of *P*-values as indicating false positive error rates when used in the context of elementary frequentist statistical theory. We still maintain, however, that one of the advantages of systematic reviews is that they can improve the precision of estimates derived from smaller similar trials, thus making lots of additional trials unnecessary when an acceptable level of false positive error has been reached. To date, 14 placebo-controlled trials of topical pimecrolimus for atopic eczema have been conducted – do we really need any more to convince the clinical community that pimecrolimus is effective when compared to vehicle? A more serious example is the use of intravenous streptokinase as thrombotic therapy for myocardial infarction. By performing a cumulative meta-analysis of similar RCTs, Lau *et al.*, (1992) showed clear and consistent benefit for streptokinase after just eight RCTs involving 2,432 patients had been performed in 1973. Yet by 1988, a further 25 RCTs involving another 35,542 patients had been performed in isolation addressing the same question without altering the risk estimate, but making the overall

P-value very small indeed ($P < 0.0001$). Such an observation illustrates the human cost of failing to observe the need to bring all evidence together within the body of a systematic reviews, as opposed to wasting valuable patient and doctor resources in continuing to perform one inconclusive trial after another. There comes a point when the likelihood of a false positive results becomes very remote, and even the most skeptical person would say "enough is enough".

CONFLICT OF INTEREST

Dr Dellavalle and Dr Williams are editor and the co-ordinating editor, respectively, for the Cochrane Collaboration Skin Group.

ACKNOWLEDGMENTS

RPD and SRF were supported by National Institutes of Health (Bethesda, MD) Grant nos. CA92550 and T32 AR07411, respectively, the University of Colorado Cancer Center (RPD), the Dermatoepidemiology Research Unit of the Department of Dermatology (RPD and SRF), and the UK NHS R&D programme (HCW).

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Novel *ABCA12* Mutations Identified in Two Cases of Non-Bullous Congenital Ichthyosiform Erythroderma Associated with Multiple Skin Malignant Neoplasia

Journal of Investigative Dermatology (2007) 127, 2669–2673; doi:10.1038/sj.jid.5700885; published online 17 May 2007

TO THE EDITOR

Non-bullous congenital ichthyosiform erythroderma (NBCIE; OMIM 242100) is a rare, autosomal recessive disorder characterized by prominent erythroderma and fine, white, superficial scales. Mutations in the transglutaminase 1

gene (Laiho *et al.*, 1997; Akiyama *et al.*, 2001; Becker *et al.*, 2003), the 12R-lipoxygenase gene, the lipoxygenase-3 gene (Jobard *et al.*, 2002), ichthyin (Lefèvre *et al.*, 2004), and FLJ39501 (Lefèvre *et al.*, 2006) have been identified as causal in human NBCIE.

Recently, mutations in the gene encoding the adenosine triphosphate-binding cassette transporter protein *ABCA12* (OMIM 607800) have been reported to cause type II lamellar ichthyosis (LI; OMIM 601277) (Lefèvre *et al.*, 2003) and harlequin ichthyosis (OMIM 242500) (Akiyama *et al.*, 2005; Kelsell *et al.*, 2005). Until now, only a few cases of autosomal recessive congenital

Abbreviations: LI, lamellar ichthyosis; NBCIE, non-bullous congenital ichthyosiform erythroderma; MM, malignant melanoma

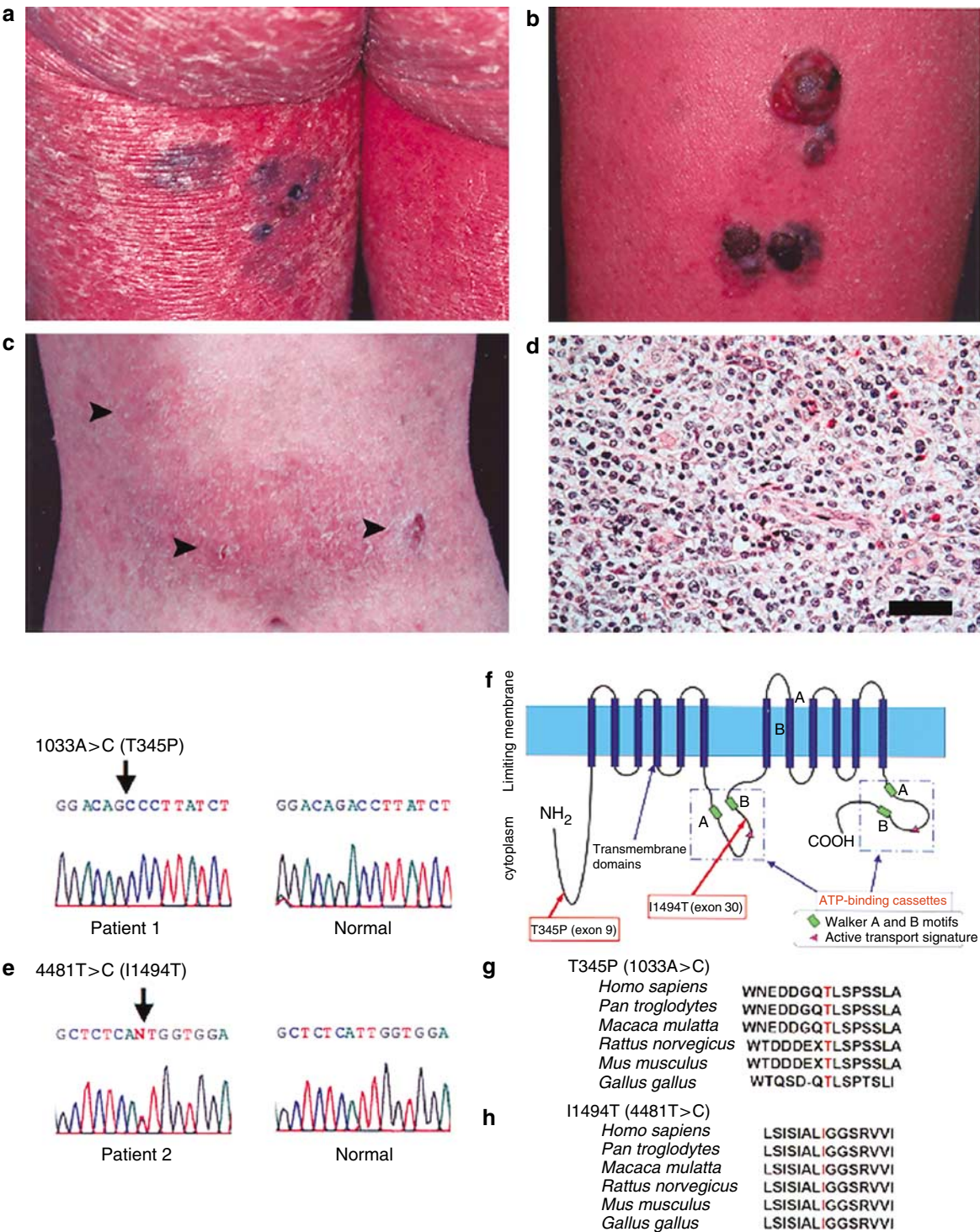
ichthyosis with *ABCA12* mutations have been reported (Akiyama *et al.*, 2006, 2007; Thomas *et al.*, 2006).

In this study, we have identified two novel *ABCA12* mutations in two unrelated NBCIE patients. Interestingly, both patients presented with multiple

skin malignancies including malignant melanoma (MM).

A 37-year-old Japanese female (patient 1) had been suffering from NBCIE from birth and had MM on her left thigh (Figure 1a). As complete resection and adjuvant chemotherapy, no recurrence

of MM had been observed for 4 years. At the age of 40, she presented with cutaneous lymphoma on her trunk (Figure 1c and d). Patient 2 was a 42-year-old Japanese man with NBCIE, who had been treated with oral retinoids for decades, and developed



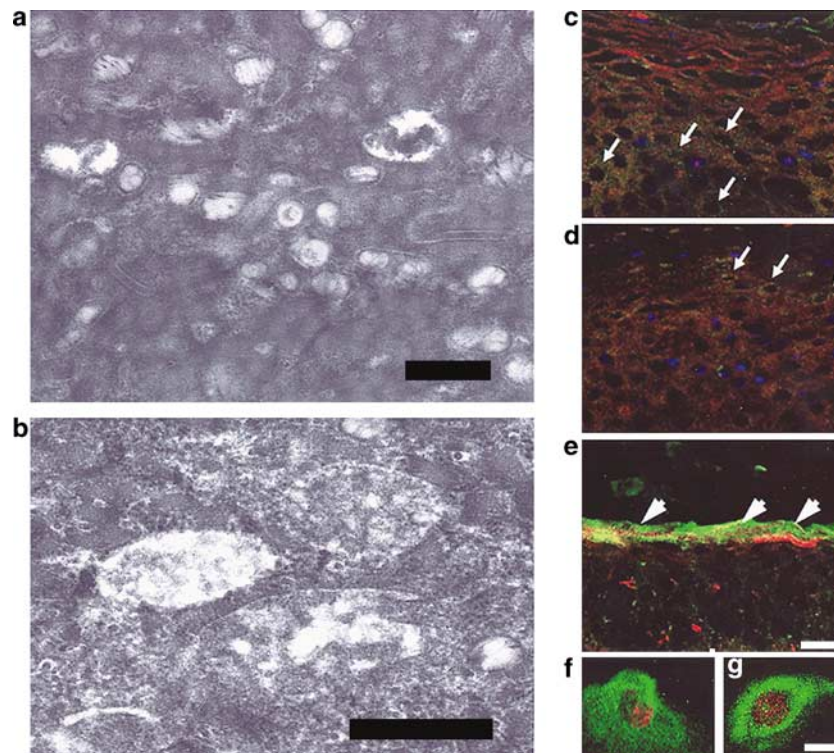


Figure 2. Ultrastructural and immunofluorescent analysis. (a and b) Abnormal lamellar granules, lipid vacuoles, and vesicles in the granular layer cells and horny layer cells of patient 1. (a) Abnormal lipid vacuoles were seen in the keratinized cells of patient 1 (bar: 0.5 μ m). (b) Large vesiculated vacuoles, putative accumulated abnormal lamellar granules, were observed in the cytoplasm of the granular layer cell of patient 1 (bar: 0.5 μ m). Abnormalities of lipid droplets in the keratinized cells in the stratum corneum were milder than those in the skin samples from typical harlequin ichthyosis patients harboring *ABCA12* truncation mutations (Akiyama *et al.*, 2005). (c-e) Double immunolabeling of ABCA12 and glucosylceramide in the upper epidermis. (c and d) Weak, diffuse ABCA12 (red) staining was seen in the cytoplasm of the upper epidermal keratinocytes of patients 1 (c) and 2 (d). Glucosylceramide (green) staining was also observed in the cytoplasm of upper epidermal keratinocytes of the patients. In some cells, glucosylceramide accumulated in the perinuclear areas (arrows). (e) In normal control epidermis, both ABCA12 (red) and glucosylceramide (green) staining were intense in the granular layers (bar: 20 μ m). These findings confirmed that the present patients have detectable amounts of ABCA12 protein, though mutated, in the epidermis, although it could not be excluded that these abnormal findings might be somewhat influenced by oral retinoid treatment taken by patient 2. (c) Patient 1; (d) patient 2; (e) normal control. ABCA12, red (TRITC); glucosylceramide, green (FITC); nuclear stain, blue (TOPRO). (f and g) Altered glucosylceramide distribution in the patient's cultured keratinocytes. (f) In normal cultured human keratinocytes, glucosylceramide (green) was diffusely observed within the cytoplasm extending to the cell periphery. (g) In keratinocytes cultured from patient 2, glucosylceramide (green) was seen mainly in the perinuclear area of cytoplasm, indicating aberrant glucosylceramide transport. Glucosylceramide, FITC (green); nuclear staining, propidium iodide (red). Bar = 10 μ m.

Figure 1. Clinical features and ABCA12 mutations of patients 1 and 2. (a) MM developed on the posterior surface of the left thigh of patient 1 at the age of 37. (b) MM developed on the flexor surface of the left thigh of patient 2 at the age of 47. Multiple black to brown-colored macules up to 25 mm in diameter with irregular borders were observed. He received a wide local excision of all tumors and dissection of inguinal lymph nodes, followed by combination adjuvant chemotherapy. No local recurrence or distant metastasis has been observed for 9 months after the operation. (c) The abdomen of patient 1 at the age of 40. Multiple erythematous nodules were observed. Nodules were partly ulcerated (arrowheads). (d) In Patient 1, at the age of 40, small- to medium-sized atypical lymphocytes, intermingled with a few histiocytes and eosinophils were infiltrated in the dermis of erythematous plaques (haematoxylin and eosin, bar: 5 μ m). The infiltrated cell phenotypes were CD3⁺, CD4⁺, CD8⁻, CD30⁻, CD56⁻. The T-cell receptor beta gene rearrangement proved the monoclonal nature of the infiltrated T cells (data not shown). Physical examination and imaging studies demonstrated no evidence of lymph node or organ involvement of lymphoma. We diagnosed the lesion as primary cutaneous CD4⁺ small/medium-sized pleomorphic T-cell lymphoma according to the WHO-EORTC classification for cutaneous lymphomas (Willemze *et al.*, 2005). She was treated with electron beam irradiation and three cycles of cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) chemotherapy, which lead to complete remission of lymphoma. At the age of 41, recurrence was observed in the skin and the gastric mucosa. She received salvage chemotherapy, resulting in a partial lymphoma remission. (e) Direct sequencing of *ABCA12* gene revealed a homozygous c.1033A>C transversion in *ABCA12* exon 9 in patient 1, but not in normal control samples. A heterozygous c.4481T>C transition was found in exon 30 of *ABCA12* of patient 2, but not in normal controls. Both the c.1033A>C transversion and c.4481T>C transition were novel missense mutations that changed a threonine residue at codon 345 to a proline residue (p.Thr345Pro) and an isoleucine residue of codon 1494 to a threonine residue (p.Ile1494Thr), respectively. (f) Schematic sequential arrangement of the domain structures of ABCA12 protein and the positions of mutations in the present two patients. Mutations in the patients were marked by red arrows. Note that the missense mutation p.Thr345Pro was located in the cytoplasmic region between the N-terminus and the first transmembrane domain and the other missense mutation p.Ile1494Thr was within the first adenosine triphosphate-binding cassette, which is thought to be important for ABCA12 lipid transporter activity. (g and h) ABCA12 amino-acid sequence alignment showed the level of conservation in diverse species of the amino-acid T345 and I1494 (red characters).

cutaneous squamous cell carcinoma on his neck the details of which have been described elsewhere (Arita *et al.*, 2003). Recurrence of squamous cell carcinoma has not been observed in the 5 years since complete resection was performed. At the age of 47, MM appeared on his left thigh (Figure 1b). Neither patient had significant family history or apparent risk factors for carcinogenesis.

To elucidate the patients' genetic abnormality, blood samples were collected. All the experiments, skin biopsies and blood sampling were performed with the patients' informed, written consent and with the institutional approval of Hokkaido University Graduate School of Medicine and Hokkaido Cancer Institute for experiments handling human matter in accordance with the Declaration of Helsinki Principles. No mutation was found in transglutaminase 1 in either case by direct sequencing analysis (data not shown). Then, the *ABCA12* gene was amplified by the methods previously reported by Akiyama *et al.* (2005). DNA sequencing of all the PCR products was carried out using an ABI PRISM 3100 genetic analyzer (ABI Advanced Biotechnologies, Columbia, MD). Mutational analysis of the entire 53 exons including the intron-exon boundaries of the *ABCA12* gene revealed a homozygous c.1033A>C transversion (p.Thr345Pro) in exon 9 in patient 1 and single mutation c.4481T>C transition (p.Ile1494Thr) in exon 30 was detected only in one allele in patient 2 (sequence according to Lefèvre *et al.* (2003)) (GenBank accession NM 173076) (Figure 1e and f), although no other mutations have been identified on the other allele thus far. The presence of both mutations was excluded in 200 alleles of 100 healthy unrelated Japanese individuals. Enzyme digestion assays and direct sequencing of RT-PCR amplification products from exon 30 mRNA confirmed that both alleles with and without the mutation c.4481T>C were expressed in the epidermis of patient 2 (data not shown). Sequencing of the entire *ABCA12* mRNA from the epidermis of patient 2 did not reveal any other apparent mutation (data not shown). These findings have excluded the possibility of a

whole or partial gene deletion affecting the other *ABCA12* allele in patient 2. *ABCA12* amino-acid sequence alignment shows that the threonine residue at codon 345 and the isoleucine residue at codon 1494 are conserved among several species (Figure 1g and h).

Electron microscopic examination of osmium tetroxide-fixed samples from lesional skin of patient 1 revealed that in the cytoplasm of granular layer keratinocytes, abnormal, defective lamellar granules were assembled together with some normal-appearing lamellar granules (Figure 2a and b). Electron microscopic findings from lesional skin of patient 2 partly showed the similar features to those of patient 1, although they were intensely influenced by long-term retinoid treatment and were not consistent in the entire specimen.

Immunofluorescence studies of patients' skin performed as previously described (Akiyama *et al.*, 1999) revealed that the intense *ABCA12* staining seen in the granular layer cells of normal epidermis was absent in the both patients' epidermis (Figure 2c-e).

Immunofluorescent staining showed that glucosylceramide, a major lipid component of lamellar granules (Holleran *et al.*, 1993; Vielhaber *et al.*, 2001; Ishida-Yamamoto *et al.*, 2004) was sparsely distributed in the upper layers of the patients' epidermis, compared with a more restricted, intense distribution in the granular layers of normal skin (Figure 2c-e).

Culture of keratinocytes from patient 2 under high- Ca^{2+} conditions (2.0 mM) induced a large number of cells to express condensed glucosylceramide staining around the nuclei, whereas culture of normal human keratinocytes under the same conditions revealed a more diffuse staining throughout the cytoplasm (Figure 2f and g).

Most *ABCA12* mutations are known to lead to harlequin ichthyosis or LI. The growing number of cases leading to three types of autosomal recessive congenital ichthyosis (NBCIE, LI, and harlequin ichthyosis) may be caused by an *ABCA12* functional deficiency. Generally, mild *ABCA12* dysfunction causes LI, and a serious loss of function leads to harlequin ichthyosis. However,

only one patient with *ABCA12* mutations was initially reported to show a NBCIE phenotype (Lefèvre *et al.*, 2003). It is now well recognized that the phenotypic differences existing between NBCIE and LI phenotypes are not gene specific and can even be found within homogeneous kindreds. The present cases further support the idea that an NBCIE phenotype can be caused by *ABCA12* mutations.

Skin neoplasia occurring in congenital ichthyosis patients, including LI (Elbaum *et al.*, 1995), Netherton's syndrome (Weber *et al.*, 2001; Saghari *et al.*, 2002; Krasagakis *et al.*, 2003), ichthyosis hystrix (Judge and McGibbon, 1994; Stratigos and Tsembalos, 1995), KID syndrome (Madariaga *et al.*, 1986; Grob *et al.*, 1987; Hazen *et al.*, 1989; Kim *et al.*, 2002; van Steensel *et al.*, 2002), and MAUIE syndrome (Elbaum *et al.*, 1995; Hendrix *et al.*, 1997), has been reported, although we cannot find any reports of MM and cutaneous lymphoma associated with congenital ichthyosis patients in the literature.

We cannot assume a direct association of *ABCA12* mutations to skin malignancy in our patients, as *ABCA12* is expressed mainly in keratinocytes, not in melanocytes or lymphocytes (Annulo *et al.*, 2002; Peelman *et al.*, 2003; Akiyama *et al.*, 2005). Defective *ABCA12* function is thought to result in malformation of intercellular lipid layers in the stratum corneum of the patients. Owing to this lipid barrier deficiency, the skin surface is likely to be easily irritated, resulting in a chronic state of inflammation. These recurrent and long-lasting irritation and inflammation processes may increase the likelihood of skin carcinogenesis, perhaps through promotion of tumor progression, although the exact mechanisms remain unknown.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

We thank the patients for their generous cooperation and Ms Akari Nagasaki for her fine technical assistance on this project. This work was supported in part by Grant-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan to M Akiyama (Kiban B 18390310).

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